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Human Toxicity of PBDDs and PBDFs

The brillant literature review and health risk assessment by Mennear and Cheng-Chung, "Polybrominated Dibenzo-*p*-dioxins and Dibenzofurans: Literature Review and Health Assessment" [*EHP* 102(suppl 1):265–274], states that "reports of human toxicity associated with exposure to PBDDs and PBDFs were not found" (p. 272). In fact, in their review, no references are discussed or quoted regarding human studies.

Two papers have been published on the human toxicology of these compounds. The first (*1*) is a recent report, previously presented at the Dioxin '90 Congress (*2*), about a chemist who was exposed to 2,3,7,8,-tetrabromodibenzodioxin (TBDD) and to 2,3,7,8-tetrachlorodibenzodioxin (TCDD) in March and September 1956, respectively, when synthesizing these chemicals. The chemist was defined as "in good health" in 1990, when determinations of chlorinated and brominated dioxins and dibenzofurans were performed on whole blood. High concentrations of several congeners were detected, and the results were used to discuss the half-life of the chemicals in humans. The subject presented a mild chloracne after an unspecified time from his exposure to bromodixoins in March, suggesting that TBDD could produce skin effects as chlorodioxins. Other more relevant symptoms occurred after the exposure to TCDD in September, and the patient was hospitalized for a short period.

The second was a study of subjects exposed to PBDDs and PBDFs as a result of working at a BASF factory in etrusion blending of polybutyleneterphthalate with decarbromodiphenyl ether, used as a flame retardant. The intensity of exposure was determined in 1989 through air monitoring (*3*). The paper presents blood levels of 2,3,7,8,-TBDF and TBDD and of total congener profiles for some exposed workers and the results of a comparison of several immunological tests in a population of exposed versus a population of unexposed deriving from the same working cohort. Workers had detectable blood levels of TBDD and TBDF; half-life estimates of these chemicals are presented. The results of immunological tests were described as "not adversely impacted at these burdens of PBDFs and PBDDs," even though the results of several tests showed a correlation with exposure, and in the subject having the highest blood levels of PBDFs and PBDDs, immunological changes were quite relevant. The authors stated that clinical examination did not reveal "skin lesions consistent with an acnegenic response."

It should be stressed that the results of the two quoted articles do not change the conclusions of Mennear and Cheng-Chung on the health risks of PBDDs and PBDFs. However, slightly different suggestions for future research can be derived. Human populations have been or are exposed to these chemicals because of their use in several work processes involving flame retardants, environmental exposures (mainly due to municipal incinerators), or because of accidents due to thermal decomposition of flame retardants. These exposed human populations can be suitable, at least in theory, for toxicological and epidemiological observations.

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Arsenic Risk Assessment

A commentary highly critical of two of our published studies was recently published in *Environmental Health Perspectives* (Carlson-Lynch et al., 102:354–356). One of our papers examines the epidemiological evidence for a methylation threshold for inorganic arsenic and concludes that there is no consistent evidence to support the hypothesis of such a threshold in humans (*1*). The second paper critiqued by Carlson-Lynch et al. estimates the human cancer risks of arsenic at internal sites (lung, liver, kidney, and bladder) using linear extrapolation from Taiwanese data (*2*). Carlson-Lynch et al. contend that the analyses conducted in our studies are flawed and that the conclusions reached in our publications are erroneous, rendering them unsuitable for use by the EPA in risk assessment.

Whether or not our studies are used by the EPA for risk assessment is of little concern to us, but we are certainly concerned about statements that they are flawed. Careful examination will show that all of the major points raised in the commentary are either incorrect or have no valid basis. We would like to respond to the criticisms made, point by point, in the order presented, beginning with the methylation paper (*1*).

Critique: The average arsenic exposures in almost all of the studies analyzed were too low to observe methylation saturation.

Response: The commentators base this statement on three issues. First, the authors state that evidence from an experimental study (of only four human volunteers each receiving only one dose level) suggests that methylation would be completely saturated at exposures greater than 500 µg/day (*3*). However, at the highest oral dose in this study, 1000 µg/day, the amount of urinary arsenic in the inorganic form was only 26%, hardly demonstrating methylation saturation even at this level. Buchet et al. (*3*) state in their paper that "speciation of the arsenic metabolites in urine indicated that the arsenic methylation capacity of the human body was not yet saturated, even with an oral daily dose of 1000 µg As." The evidence of *any* metabolic saturation from this study is not conclusive. Each of four arsenic dosing levels was assigned to a different individual subject, making it impossible to differentiate interindividual differences in methylation efficiency from dose-dependent effects that might apply to a general population.

Second, the authors state that we analyzed only two groups with average urinary arsenic levels at or above 190 µg/l, which they hypothesize corresponds to the concentration above which methylation saturation occurs. This statement obscures the fact that 1) the two groups combined had a total of 35 people, 2) our analysis of available individual data (see Figure 2 of our paper) included 14 persons with urinary arsenic levels >190 µg/l. No trend of higher relative proportions of unmethylated arsenic is suggested for those 14 individuals.

Third, the authors state: ". . . a regression analysis on the individual data within the Yamauchi et al. [*4*] population was borderline significant at $p = 0.10$. . ." (p. 354). However, this was just one of nine regression analyses we presented. The slopes were positive in four (including the Yamauchi study) but negative in five (*1*: Table 9).

As a matter of interest, in our more recent studies of chronically exposed popu-